PHARMACEUTICAL ANTIHERPETIC COMPOSITION

The present invention relates to the field of biomolecular pharmacology, particularly to the provision of a new pharmaceutical antiherpetic composition.

At present the following preparations against herpes virus are known: Acyclovir, Virazol, Foscarnet, Vidarabin, and others [1]. However, chemotherapeutic means are not always sufficiently effective, because they do not have a specific action with regard to herpes virus only, in principle are polyactive , and can be used in other virus diseases,.

Corresponding vaccines have specific activity with regard to herpes virus. A number of antiherpetic vaccines, including those based on inactive virions, have been developed both in Russia and in other countries. For example, such vaccines are described in Russian Federation Patents No. 2014084, 1994, No. 2085582, 1997, No. 2085583, 1997, in US Patents No. 4816250, 1989, No. 5215745, 1993, No. 5602023, 1997.

Though the vaccines cited in these documents are specific and prepared on the basis of inactivated and attenuated strains of herpes virus, not all of them are fit for treating humans. For the virus combating in a highly organized organism to be successful, it is necessary to take into account humoral and cellular factors, the condition of the immune system, the degree of affliction by the virus, the stage of the disease (latent infection, acerbation), the psychophysical condition of a human.

The known mechanisms of action of the herpes virus on immunocompetent cells and on the immune status on the whole suggest that into antivirus preparations compounds shall be included, which specifically influence the immune system, as well as substances normalizing the cellular metabolism, when an organism has been afflicted by herpes simplex virus, especially in cases of sluggish, recurrent diseases, diseases that poorly answer to therapeutic treatment, have a tendency to chronization. It is expedient to include into the complex therapy immunocompetent substances, such as interferons and antioxidants, as recommended in our previous inventive developments (see, e.g., Russian Federation Patent No. 2142816, 1999), where one of dosage forms convenient for a patient (in the form of as suppository) is also shown. We regard said inventive development as the closest analog of the present invention. In spite of considerable advantages offered by the above-named vaccine preparation, some important aspects of the condition of the patient's organism afflicted by herpes virus are not taken into account therein. In patients with chronic forms of the disease a disturbance of the cellular and humoral immunity is observed, an

enhanced secretion of glucocorticoids and a sharp disturbance of the metabolism of the virus-affected cells and tissues take place.

It is known that in higher animals the immune system is necessary for combating infectious diseases, that is, simplest live pathogens: bacteria, microbes, fungi, viruses, and the like. Does immunity exist in invertebrates, for instance, in insects? Searches for an answer to this question have led to a discovery of a new class of unique substances.

Insects do not possess an immune system similar to the one mammals have. In insects substances are generated which are capable of blocking foreign proteins which got into their organism. However, it has been known long since that insects can combat pathogenic microorganisms. In 1980 a group of researchers headed by Hans Bohman of the Stockholm University (Sweden) succeeded in establishing the following: a bacteria-infected solution was injected to a larva of the Hyalophora secropia moth, and then the substances secreted by the infected larva were collected and analyzed. As a result, the scientists obtained two new chemical compounds — peptide molecules consisting of 35 to 39 amino acids. They were given the name of cecropins [2].

In principle, antimicrobial substances which comprise molecules of 20 to 40 amino acids have been known long since. More than half a century ago antimicrobial peptides gramicidin and nisin were isolated, which are widely used in pharmaceutical and food industry. Antibacterial phytopeptides and peptides from apitoxin were described long ago. Nevertheless, Bohman's discovery provoked interest. In the first place, the isolated peptides at first sight were much like the well-known substance melittin contained in apitoxin, but with one small difference: unlike melittin, cecropins killed the cells of the Escherichia coli type only (of so-called gram-negative bacteria) and did not act on other microorganisms or on the cells of higher organisms. The opinion predominant among researchers was that antimicrobial peptides are produced by the secretory organs of lower animals which do not have a developed immune system. It was shown that mammals — rabbits, cows and even humans — can also secrete similar substances. This occurs predominantly in the area of the intestine, the respiratory tract and the ureters. Peptides are constantly produced even in the quiescent state of an organism, but when the organs are infected or damaged, a burst of the synthesis of peptides takes place.

Antimicrobial peptides, though they are somewhat inferior to antibiotics in effectiveness, act much faster and, this being of crucial importance, they destroy bacteria which are resistant to the known antibiotics. However, only those peptides can be used clinically as antibiotics and antifungal agents, which do not hemolyze the cells of mammals. Said peptides can "do away " with viruses in different ways. In the first place, some of them

simply interact with a virus directly, blocking its activity. In this manner they inactivate, e.g., stomatitis and even HIV viruses. In the second place, peptides can block the multiplication of HIV virions in an infected organism. Cecropins and melittin act in this way [3].

It is a technical object of the present invention to provide a new, more effective and advanced comprehensive preparation which would not only selectively and strongly act on herpes simplex virus, but also provide an intensive immunomodulating effect on an organism as a whole, and also normalize the metabolism in virus-affected cells and tissues.

Said object is accomplished by that a virion vaccine antiherpetic preparation, wherein viruses of herpes simplex of serotypes 1 or 2 inactivated by formalin or γ-radiation and an acceptable physiological solution are comprised, further comprises polyoxydonium, and also valine, lysine, isoleucine, as well as a combination consisting of at least 2 amino acids selected from the group consisting of phenylalanine, leucine, alanine, threonine, histidine, arginine, methionine. The pharmaceutical composition has the following ratio of the components:

antiherpetic preparation — 10^6 to 10^7 plaque-forming units/ml

polyoxydonium	0.03—0.06 g
valine	0.18—0.25 g
lysine	0.15—0.30 g
isoleucine	0.11—0.22 g
combination of 2 metabolic amino acids	0.12—0.27 g
physiologically acceptable solution	to 100 ml

The composition may further comprise a number of solid, soft, liquid adjuvants or a mixture thereof.

The composition may further comprise a combination of 2—3 water- and fat-soluble vitamins selected from the group consisting of thiamine, riboflavin, nicotinamide, pyridoxine, ascorbic acid, retinol, tocopherol, or their mixtures in a total amount in the formulation of the composition of from 0.05 to 3.5%.

Such preparation is suitable in treating herpes simplex of types 1 and 2. For this purpose a combination of amino acids and vitamins corresponding to each kind of herpes is selected, the dosage and schedule being selected depending on the condition of a patient.

Our investigations have shown that the best effect for test subjects with different forms of herpes is the high-technology synthetic preparation polyoxydonium (PO) [4].

In vivo conditions PO produces a more sophisticated and multi-aspect effect on the immune system. Since the development of any immune response commences with the

cells of the monocyte/macrophage system, and since cytokines produced by monocytes/macrophages have a pleiotropic effect, an enhancement of their functional activity under the influence of PO leads to activation of both cellular and humoral immunity. Thus, in particular, upon administering PO jointly with low doses of an antigen there takes place a 5- to 10-fold enhancement of the synthesis of antibodies to this antigen as compared with control. It is important to note that such enhancement can be observed in animals with a genetically determined weak reaction to the given antigen. Hence, PO has a capacity of driving all the factors of organism protection from foreign agents of antigen nature, and this deriving propagates in a natural manner so as this occurs in the development of immune response in an organism. These observations have enabled us to stop our selection among a large number of present-day immunomodulators exactly at polyoxydonium for its successful use in the formulation of a complex pharmaceutical antiherpetic composition. We have succeeded to establish empirically that very effective components in the formulation of the composition are essential amino acids valine and lysine, and also certain amino acids which lead to the acceleration of epithelialization of virus-affected cutaneous tissue. Such a composition, especially with the addition of microelements, which enhances immune response to the administration of the preparation, makes it possible to use the composition also for a more effective combating virus lesions caused by herpes of serotypes 1 and 2. A detailed description of the influence of microelements in the immune system is given in our earlier filed application.

It should be noted that the incorporation into the composition of amino acids (valine and lysine and, besides, a composition consisting of at least 2 amino acids selected from the group: phenylalanine, leucine, alanine, threonine, histidine, arginine, methionine) in al the combinations proposed by us accelerated the reepithelialization of affected tissues (from 15 to 30% over the prototype) depending on the kind of virus.

The incorporation into the formulation of the composition of an essential amino acid, isoleucine, is of special importance for the present invention.

Isoleucine has a unique property which has been used in the formulation of an antiherpetic composition for the first time: this amino acid obtained only from the outside (for example, with food) stimulates the production in a human organism (predominantly in the intestine area) of antimicrobial peptides, similar to cecropins, which are capable of destroying herpes viruses.

The present invention is illustrated by the following.

Our numerous experiments on animals: rabbits and guinea pigs have shown that adding isoleucine to the composition significantly enhances the effect of healing herpetic

lesions as compared with the use of the composition without adding this particular amino acid. In rabbits, in the case of experimental herpes keratitis, and in guinea pigs, in the case of genital herpes, the healing takes place, respectively, 10—12% and 9—15% of time earlier (as compared with our earlier filed application).

Other amino acids employed by us have the following properties, apart from the generally known ones, which we had taken into account when selecting amino acids for our purposes.

Histidine — enters into the composition of carnosine and anserine, plays an important role in the formation of hemoglobin, is necessary for the generation of erythrocytes. It contributes to controlling the sugar level in blood and to producing energy.

Leucine — is necessary for the growth and healing of bones, muscles. In the metabolism of leucine energy is released, it contributes to stabilization of sugar level in blood. It is found that leucine deficiency in some cases may provoke hypoglycemia, retardation of growth, reduction of bodyweight, changes in kidneys and in the thyroid gland.

Lysine — strengthens the immune system, contributes to the growth of bones and formation of collagen, improves attention, has direct anti-herpetic activity. Shortage of lysine in diet leads to disturbance of blood circulation (the number of erythrocytes decreases, the content of hemoglobin in them diminishes). Deficiency may lead to the emaciation of muscles, to disturbance of bone calcification, changes in the liver and lungs, especially in aged and gerontic patients.

Methionine — is used for the synthesis of choline, is known as a "lipotropic agent", because it reduces the stock of fats in the liver and in an organism as a whole and lowers the amount of cholesterol. Creates new bone tissue, inhibits onchypathies, protects kidneys and is a natural chelating agent for heavy metals. Methionine is of great importance for the functions of adrenal glands and for the synthesis of adrenalin, this being crucial for metabolic control in virus-affected cells.

Penylalanine — is associated with the function of thyroidal gland and adrenal glands, participates in the formation of a core for the synthesis of thyroxin which is the main hormone of the thyroid gland, participates in the formation if adrenalin. In the organism phenylalanine can be transformed into thyrosine which is used for the synthesis of two main neurotransmitters, dopamine and epinephrine controlling cell metabolism on the neurohumoral level. Phenylalanine is effective in controlling pain and itch sensations. Besides, owing to the secretion of cholecystokinin, phenylalanine has appetite-suppressing action.

Valine —valine deficiency may lead to damage of the myelinic coating of nerve fibers and to the origination of negative hydrogen balance of the organism, this being extremely dangerous for virus-infected paticnts.

Alanine — strengthens the immune system participates in glucose metabolism.

Arginine — shortage of arginine may cause loss of hair, constipations, hepathopathies, and slow healing of wounds, including those caused by affection with virus toxins.

Important complements to the present invention are different dosage forms in which our composition can be practically employed.

The composition is prepared by conventional methods with the help of the following techniques:

The composition can be embodied as dosage forms in which solid, soft or liquid substances can be used as a carrier. The final form of the composition with the use of solid carriers comprises a tablet, dragee, granule, sachet or powder placed into a capsule.

The final product produced from the composition with the use of liquid carriers comprises a solution, gel, emulsion, suspension, potion, syrup or liniment. The composition with the use of soft carriers comprises an ointment, crème, paste, suppository, implant or chewing tablet, or pastille.

The composition comprises active components, adjuvants required for preparing a certain pharmaccutical form, mixed by following a conventional technology, and further comprises 2—3 microelements selected from the group: zinc, chromium, selenium and nickel. The set of microelements are introduced into the formulation of the dosage form as soluble chelate forms in an amount of 0.01—0.08% for the total mass of the dosage form.

The pharmaceutical antiherpetic composition ca be used by introducing it into a herpes virus-affected organism in an effective dose as a suitable dosage form in a suitable way selected from the group orally, sublingually, intranasally, rectally, vaginally, parenterally, subconjunctivally.

Further it is explained, how on the basis of our composition different pharmaceutical forms suitable for use can be prepared.

EXAMPLE 1

Tablets — a dosage form produced by pressing active substances and adjuvants, intended for ingestion, external, sublingual, implantation or parenteral application. Granules ca also be assigned to the same group of solid dosage forms. Granules — a dosage form for ingestion in the form of round, cylindrical or irregular globules, comprising a mixture of active compounds and adjuvants. Granules may be encapsulated.

As adjuvants use can be made of alginic acid and its sodium salt, acetyl cellulose, acetylphthalyl cellulose and its sodium salt, aerosil, water, wax, glycol, glucose, dextrin, gelatin, kaolin, carboxymethyl cellulose (CMC) and its sodium salt, tartaric acid, citric acid, stearic acid and its calcium and magnesium salts, starch, magnesium carbonate, magnesia, mannitol, vaseline oil, vegetable oil, methyl cellulose, microcrystalline cellulose (MCC), wheat flour, sodium hydrocarbonate, sodium chloride, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), natural gums, ruberosum, sugar, lactic sugar, sorbitol, Tween-80, titania, tropeolin 0, flavorosum, cerulesum, ethyl cellulose, shellac, and other substances.

Tablets for different ways of application can be prepared:

1. Peroral tablets, wherein active substances are released in the gastrointestinal tract (GIT): gastrosoluble (soluble in the stomach), enterosoluble (soluble in the intestine), dulciblettae — tablets for chewing (assimilable, starting with the mouth cavity), sculiblettae (buccal tablets), sublingual, irgiblettae — batch tablets.

2. Injectabulettae — aceptically prepared tablets which are dissolved in an aceptically prepared solution. The tablets are individually bottled. Ampoules with the solution are attached.

3. Implantabulettae — tablets for implanting (subcutaneously, intramuscularly). The tablets dissolve during 6—12 months. The tablets must be sterile and individually packaged. The preparation of tablets comprises compaction of a loose material (a batch of the dry ingredients of our composition), introducing the necessary adjuvants, and pressing till the final product is formed — a tablet which has strength, porosity, density, moisture permeability. The tablets and granules may contain additional adjuvants.

ADHESIVE SUBSTANCES

Starch flour paste, 3—15%; sugar syrup, to 64%; solutions of gums, gelatin, 5—10%; Na CMC, 1% solution.

Ethyl cellulose, 4—8% solution; hydroxymethyl cellulose, zein, 5% solution; PVP, solution to 10%; polyethylene glycol (M.M. 4000, 6000), 1—3.5% solutions.

For tablets and granules the following *colorants* are employed:

Indigo, Red 2C, tropeolin 00, eosin, ruberosum, carotene, chlorophyll, erythrosine, amirint.

The formulation of tablets and granules may include *prolongators* which extend the action of the active composition to 24 hours: mono- distearin, mono- diglycerides, white wax, palm oil, cellulose phthalate, paraffin, 3-laurin, sunflower oil.

Besides, solid dosage forms may contain DILUENTS: glucose, sucrose, lactose, starch, dextrin, glycine, basic magnesium carbonate, basic calcium carbonate, sulfate, phosphate, urea, and also polyatomic alcohols: mannitol, xylitol, MCC.

Tablets and granules may contain *DEBONDING AGENTS* which :ensure rapid mechanical degradation of tablets upon contact with liquids, because they increase the total contact surface of the liquid phase and the solid. These agents enhance absorption of active components. In terms of their mechanical action these agents are classified as: gas-forming, swelling, improving the wettability and water permeability of tablets.

Gas-forming agents act upon contact with water, there takes place the reaction of interaction of tablets with water, and gases evolve which disrupt the solid dosage form (for example, the filler is a mixture of tartaric acid and sodium carbonate or calcium carbonate).

Swelling agents swell upon contact with water. Amylopectin, agar-agar, alginic acid, gelatin, cellulose derivatives (MCC, Na MCC , aerosol)

Substances improving *wettability and water permeability*: nonionogenic surfactants — become adsorbed on particles, Tween-80 (not over 1%), starch, and also mixtures: starch (imbibes water) + Na MCC (swells).

Tablets may contain *GLIDANTS*: talc, finely ground dried starch, defatted milk powder, PEG (M.M. 400—600), aerosil (particle diameter 40 nm), talcumin, Antiadhercnts (lubricants) are hydrophobic substances, they reduce friction on the surface of particles. They increase the disintegration time of tablets, because, as the pressure increases, they melt and form films. To such substances there belong: stearic acid and its salts, solid paraffins, fats, vaseline, ceresin, silicones (not over 1%). Combined-action glidants: (talc + calcium stearate).

EXAMPLE 2

Capsules — a dosage form consisting of a medicament enclosed in an envelope. Capsules are intended for intaking, as well as for rectal and vaginal administration. Two types of capsules are distinguished: solid, with small lids (Capsulae durae operculatae) and soft, with an integral envelope (Capsulae molles). For preparing a capsule envelope use is made of gelatin, water and various adjuvants (glycerin, sorbitol, sugar, titania, Acid Red 2C, tropeolin 0, sodium metabisulfite or potassium metabisulfite, Nipagin, and others) allowed for medicinal use. The contents of capsules consist of active components of the composition with optional incorporation of various adjuvants allowed for medicinal use. The contents of a capsule can be solid, liquid or paste-like. Capsules must have a smooth surface, without injuries and visible air and mechanical inclusions.

Solid capsules, depending on their capacity, can be manufactured of eight size numbers — from 000 (maximum size) to 5 (minimum size), see the Table.

Table

No.	000	00	0	1	2	3	4	5
Average capacity of capsules, ml	1.37	0.95	0.68	0.5	0.37	0.3	0.23	0.13

Soft capsules can have a spherical, egg-like, elongated or cylindrical shape with semi-spherical ends, with a seam or without a seam. Capsules can be of different sizes, with a capacity of up to 1.5 ml. For our composition the optimal capacity of capsules is 0.5 — 1.2 ml. The envelope of soft capsules can be rigid or elastic, depending on the purpose of using a capsule.

EXAMPLE 3

Eye drops — a dosage form intended for instillation into eyes. Eye drops must be isotonic with the lacrymal fluid. As stabilizers, preservatives, prolongators and other adjuvants use is made of sodium chloride, sodium sulfate, sodium nitrate, sodium metabisulfite, sodium thiosulfate, mono- and disubstituted sodium phosphates, boric acid, sorbic acid, nipagin, cellulose derivatives, and others. Eye drops must be prepared in aseptic conditions and be sterile.

EXAMPLE 4

MEDICAMENTS FOR PARENTERAL ADMINISTRATION

To medicaments for parenteral administration there belong sterile aqueous and non-aqueous solutions, suspensions, emulsions and dry substances (powders, porous masses, tablets) which should be dissolved in a sterile solvent directly before administering. As solvents use is made of water for injections, fatty oils, ethyl oleate. In the formulation of a complex solvent use can be made of ethyl alcohol, glycerin, propylene glycol, polyethylene oxide 400, benzyl benzoate, benzyl alcohol, and other solvents.

EXAMPLE 5

Ointments — a soft dosage form intended for applying to the skin, wounds or mucous membranes. An ointment consists of a base and a pharmaceutical composition uniformly distributed in the base. For preparing an ointment with our composition, bases allowed for medicinal use are employed: lipophilic — hydrocarbon bases (vaseline, fusions of hydrocarbons), fatty bases (natural, hydrogenised fats and their fusion with vegetable

oils and fat-like substances), silicone bases and others; hydrophilic bases — gels of high-molecular hydrocarbons and proteins (ethers of cellulose, starch, gelatin and agar), gels of inorganic substances (of bentonite), gels of synthetic high-molecular compounds (of polyethylene oxide, polyvinyl pyrrolidone, polyacrylamide) and others; hydrophilic-lipophilic bases — anhydrous fusions of lipophilic bases with emulsifiers (a fusion of vaseline with lanolin or other emulsifiers), emulsion bases of water/oil type (a fusion of vaseline with aqueous lanolin, a consistent water/vaseline emulsion, and others) and oil/water (as emulsifiers use is made of sodium, potassium, triethanolamine salts of fatty acids, Tween-80) and others. Into ointments preservatives, surfactants and other adjuvants allowed for medicinal use may be incorporated.

EXAMPLE 6

Plasters — a dosage form for external application, having an ability of adhering to the skin. Plasters act on the skin, on the subcutaneous tissues, and in our case they produce also a systemic action on the organism. Plaster can be in the form of a plastic mass on a support or without it, or in the form of a liner with the formulation of our composition, secured on an adhesive tape. The formulation of the plaster mass may comprise as adjuvants substances allowed for medicinal use: natural or synthetic rubbers, mixtures thereof, and also other polymers, fat-like substances, natural oils, fillers and antioxidants. The plaster mass in appearance is a homogeneous mixture, which is dense at room temperature and softens at a body temperature.

EXAMPLE 7

Powders — a solid dosage form for internal and external application, consisting of the comminuted substances of our composition and having the property of flowability. Powders divided and not divided into separate doses are distinguished. The powder of our composition belongs to the category of compound powders, it is prepared with taking into account the properties of the ingredients and their amounts. When the ingredients are present in the formulation of a compound powder in different amounts, blending is started with substances entering in the formulation in smaller amounts, the rest of the ingredients being added gradually.

EXAMPLE 8

Syrups — concentrated aqueous solutions of sucrose, which may contain medicinal substances, nutritional fruit extracts. Syrups are thick transparent liquids, having, depending on their formulation, characteristic taste and odor. Syrups are prepared by dissolving sugar under heating in water or in extracts from vegetable stock. Medicinal syrups are also prepared by adding medicinal components to a sugar syrup. The resulting syrups are

filtered and dispensed into dry sterile containers. When necessary, preservatives (alcohol, nipagin, sorbic acid, nipasol) or other preservative agents allowed for medicinal use are added to syrups.

EXAMPLE 9

Suppositories — dosage forms that are solid at room temperature and melt at a body temperature. Suppositories are used for introducing into body cavities. Rectal suppositories (Suppositoria rectalia), vaginal suppositories (Suppositoria vaginalia) and rod-like suppositories (bacilli) are distinguished. Rectal suppositories can be shaped as a cone, as a cylinder with a pointed end, or have a different shape. Vaginal suppositories can be spherical (globuli), egg-shaped (ovula), or shaped as a flat body with a rounded end (pessaria). As lipophilic bases for producing suppositories use is made of cocoa oil, fusions of cocoa oil with paraffin and hydrogenated fats, vegetable and animal hydrogenated fats, hard fat, Lanol, fusions of hydrogenated fats with wax, solid paraffin, and other bases allowed for medicinal use. As hydrophilic bases use is made of gelatin-glycerin gels, fusions of polyethylene oxides with different molecular masses, and other substances allowed for medicinal use. The gelatin-glycerin base is prepared from medicinal gelatin, glycerin and water. When preparing suppositories, use can be made of butylhydroxytoluene, butylhydroxyanisole, citric acid, emulsifier No. 1, emulsifier T-1, emulsifier T-2, Tween-80, wool wax alcohols, aerosol, and other adjuvants allowed for medicinal use. The active compounds, when necessary, are comminuted, sifted, mixed with a base directly before or after dissolution in or trituration with a small amount of water, glycerin, vaseline oil or other suitable solvent. A method for preparing one of possible kinds of suppositories with the use of our composition is described in our earlier filed Application No. 2003131814.

EXAMPLE 10

Suspensions — a liquid dosage form containing as a disperse form one or more comminuted powder-like medicinal substances distributed in a disperse medium. Suspensions for internal, external and parenteral administration are distinguished. Suspensions for parenteral administration are introduced only intramuscularly.

EXAMPLE 11

Emulsions — a dosage form uniform in appearance, consisting of mutually insoluble finely dispersed liquids, which is intended for internal, external or parenteral administration. Emulsions, as a rule, are stabilized by emulsifiers. In emulsions peach-kernel oil, olive oil, or sunflower oil are used.

EXAMPLE 12

The results of testing different forms on a group of 152 experimental animals (herpes conjunctivitis in rabbits, genital herpes in guinea pigs) have shown that the use of the new preparation not only activated the immunity, but also allowed the remission period to be appreciably prolonged, the process of reepithelialization and healing of the skin and mucous tissues to be accelerated, and in some cases to succeed in practically curing the disease in separate individuals (15% of all the test individuals with chronic form of the disease). In our opinion, a role of no little significance in this result was played by the incorporation into the formulation of the dosage form of vitally important ingredients which regulate metabolic processes on all levels, namely: polyoxydonium, valine, lysine, isoleucine, vitamins of all groups, and also a set of microelements from the group: zinc, chromium, selenium and nickel.

EXAMPLE 13 *Main Performance Criteria.* The time of attaining topical convalescence (complete reepithelialization) reduced by 15—36%, the duration of remission increased on an average to 7.5% months, the absence of virus in the smear (PCR-diagnostics) in 99.7% of cases, activation of the antivirus immunity, practically complete curing in 15% of the follow-ups of the animals (in animals with chronic forms).

Owing to the provision of the new highly immunogenic composition influencing the metabolism of affected cells and the generation of antiherpetic toxins by healthy cells, the antigenicity and stability of the specific activity of the preparation are preserved, not only the antivirus properties are enhanced, but the organism resistance is increased and prolonged in cases of an acute and even chronic infection.

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